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Management patterns of non-ST segment elevation acute coronary syndromes in relation to prior coronary revascularization

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Background Contemporary guidelines support an early invasive strategy for non-ST elevation acute coronary syndrome (NSTEMI-ACS) patients who had prior coronary revascularization. However, little is known about the management pattern of these patients in "real world."

Methods We analyzed 3 consecutive Canadian registries (ACS I, ACS II, and Global Registry of Acute Coronary Events [GRACE]/expanded-GRACE) that recruited 12,483 NSTEMI-ACS patients from June 1999 to December 2007. We stratified the study population according to prior coronary revascularization status into 4 groups and compared their clinical characteristics, in-hospital use of medications, and cardiac procedures.

Results Of the 12,483 NSTEMI-ACS patients, 71.2% had no prior revascularization, 14.2% had percutaneous coronary intervention (PCI) only, 9.5% had coronary artery bypass graft surgery (CABG) only, and 5% had both PCI and CABG. Compared to their counterparts without prior revascularization, patients with previous PCI and/or CABG were more likely to be male, to have diabetes, myocardial infarction, and heart failure but less likely to have ST-segment deviation or positive cardiac biomarker on presentation. Early use of evidence-based medications was higher among patients with previous PCI only and lower among patients with previous CABG only. After adjusting for possible confounders including GRACE risk score, prior PCI was independently associated with in-hospital use of cardiac catheterization (adjusted odds ratio [OR] 1.18, 95% CI 1.04-1.34, $P = .008$). In contrast, previous CABG was an independent negative predictor (adjusted OR .77, 95% CI 0.68-0.87, $P < .001$). There was no significant interaction ($P = .93$) between previous PCI and CABG.

Conclusions The NSTEMI-ACS patients with previous PCI were more likely to be treated invasively. Conversely, patients with prior CABG less frequently received invasive therapy. Future studies should determine the appropriateness of this treatment discrepancy. (Am Heart J 2010;159:40-6.)

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^hA list of participating Canadian ACS Registry I and II investigators and coordinators can be found in Arch Intern Med 2007;167:1009-1016.

ⁱA list of participating Canadian GRACE and expanded-GRACE investigators and coordinators may be found Am Heart J 2009;157:642-650.

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Coronary heart disease is a major cause of morbidity and mortality worldwide. Although percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) are 2 fundamental treatment modalities for coronary heart disease, patients remain at risk for adverse cardiovascular events even after successful revascularization. The growing number of acute coronary syndrome (ACS) patients with prior coronary revascularization demands the implementation of robust evidence-based management strategies to optimize clinical outcomes. Yet, patients with prior coronary revascularization, especially those with prior CABG, have often been underrepresented in or excluded from clinical trials.¹⁻³

Current American College of Cardiology/American Heart Association guidelines⁴ support an early invasive

strategy in non-ST elevation ACS (NSTEMI-ACS) patients without serious comorbidity who had PCI in the past 6 months or prior CABG. However, there are limited data on the management pattern of these patients in the “real world.” Accordingly, we used data from the Canadian Global Registry of Acute Coronary Events (GRACE/expanded-GRACE), Canadian ACS Registries I and II to examine the medical treatment and use of invasive cardiac procedures in relation to prior revascularization among NSTEMI-ACS patients.⁵⁻¹⁰

Methods

Study design

Details of the Canadian Acute Coronary Syndrome Registries (ACS I and ACS II)^{9,10} and the Global Registry of Acute Coronary Events (GRACE/expanded-GRACE)⁵⁻⁸ have been previously described. Briefly, the Canadian ACS Registries were prospective, multicenter, observational studies focusing on the epidemiology, management practices, and outcomes of ACS.⁹ In ACS Registry I, 51 Canadian hospitals provided data during the period between September 1999 and June 2001. Thirty-six Canadian centers participated in the ACS Registry II and recruited patient from October 2002 to December 2003. In these registries, patients were eligible⁹ if they were (1) aged ≥ 18 years on presentation, (2) admitted to hospital with symptoms qualifying for ACS within 24 hours of onset, and (3) the qualifying ACS was not precipitated by a major comorbidity, such as gastrointestinal bleeding or trauma. To minimize selection bias, no other exclusion criteria were applied.

GRACE was a prospective multinational registry of patients with the full spectrum of ACS.^{5,6,8} Expanded-GRACE was an expansion of GRACE that was started in 2003 to provide opportunities for additional hospitals to enroll their ACS patients.⁷ In total, 53 Canadian hospitals participated in the GRACE/expanded-GRACE from 1999 to 2007. Eligible patients were (1) ≥ 18 years of age and alive on presentation to hospital; (2) admitted to the hospital with symptoms consistent with acute cardiac ischemia within 24 hours of onset with at least one of the following: electrocardiographic changes indicating ACS, increased biochemical markers of myocardial necrosis, or documented evidence of coronary artery disease; and (3) symptoms were not precipitated or accompanied by a serious concurrent illness. To reduce any selection bias and to enhance the generalizability of the findings, GRACE and expanded-GRACE recruited the first 10 to 20 patients per month if there were >120 eligible patients admitted to these hospitals in 1 year. In all 3 registries, patients were diagnosed with ST-segment elevation myocardial infarction (MI) if they had presumably new 1-mm ST-segment elevation on 2 contiguous leads or new left bundle branch block on their electrocardiogram and abnormal cardiac biomarker. Because our focus is the use of invasive strategy in the management of NSTEMI-ACS, we excluded patients with ST elevation MI and those with a final non-ACS diagnosis in this study. Of the Canadian hospitals participating in ACS Registries I and II and GRACE/expanded-GRACE projects, 29.4%, 33.3%, and 38.3%, respectively, had on-site facilities to perform coronary angiography.

Data on patient demographics, clinical characteristics, in-hospital management, and outcomes were collected by trained

coordinators using standardized case report forms. The case report forms were scanned or completed in a Web-based manner and saved in an electronic central database for each registry. Data checks were performed centrally with incomplete or potentially incorrect data returned to the original sites for revision and correction. Where required, the institutional review board approved the study and participating patients provided informed consent.

To avoid any potentially duplicate patients between Canadian ACS Registries and GRACE/expanded-GRACE, the GRACE/expanded-GRACE data used in this study included only the period from January 2004 to December 2007. Therefore, this study included 3,228, 1,956, and 7,299 NSTEMI-ACS patients, respectively, in Canadian ACS I, ACS II, and GRACE/expanded-GRACE, totaling 12,483 patients.

Patient stratification

We categorized our study cohort ($n = 12,483$) on the basis of prior coronary revascularization status into 4 mutually exclusive groups: (1) no prior PCI or CABG, (2) prior PCI only, (3) prior CABG only, and (4) both prior PCI and prior CABG. We calculated the GRACE risk score, which is a previously validated predictor of in-hospital mortality (c-statistic = 0.83) for each patient.^{8,11,12} Briefly, the GRACE risk score is composed of age, heart rate, systolic blood pressure, Killip class, cardiac arrest, ST-segment deviation, serum creatinine level, and cardiac biomarker status on presentation. The GRACE risk score categories are low (≤ 108), intermediate (109-140), and high (141-372), and the estimated risks of in-hospital death are $<1\%$, 1% to 3%, and $>3\%$, respectively.¹³ We could not determine the GRACE risk score in 9.7% of the study population due to incomplete data.

Statistical analysis

Continuous variables are reported as medians with 25th and 75th percentiles, whereas frequencies and percentages are used for categorical variables. Comparisons of continuous and categorical variables between the different groups were made by Kruskal-Wallis test and χ^2 test, respectively. We performed multivariable logistic regression to determine the adjusted odds ratios and 95% CI for the in-hospital use of cardiac catheterization in relation to prior coronary revascularization. To determine their independent association, we adjusted for variables (ie, female sex, registry, GRACE risk score, presence of on-site cardiac catheterization facilities, coronary revascularization status, prior stroke, congestive heart failure, and MI) previously shown to be associated with in-hospital use of cardiac catheterization¹⁴⁻¹⁹ and used generalized estimating equations to account for the clustering of patients within hospitals. Variables not associated with cardiac catheterization ($P > .05$) were removed by backward elimination. To determine whether prior revascularization by both PCI and CABG would be associated with different treatment strategies, we tested for their interaction in the multivariable model. Model calibration and discrimination were evaluated by Hosmer-Lemeshow goodness-of-fit test and c-statistic, respectively. A sensitivity analysis was performed by excluding patients who died within the first 48 hours of admission, as they might not have a chance to undergo cardiac catheterization. Statistical analyses were

Table I. Baseline characteristics of study population stratified into 4 groups

Characteristic	Overall	No prior PCI/CABG	Prior PCI only	Prior CABG only	Prior PCI and CABG	P (4-group comparison)
No. of patients (%)	n = 12483	n = 8884 (71.2%)	n = 1773 (14.2%)	n = 1193 (9.6%)	n = 633 (5.1%)	
Age, y*	68 (57-77)	67 (56-77)	66 (57-75)	72 (63-78)	70 (62-77)	
Female sex	34.4%	37.1%	32.1%	23.5%	24.1%	<.001
Current smoker	22.4%	24.4%	20%	15.3%	14.4%	<.001
Dyslipidemia	54.5%	45.4%	76.2%	75.2%	82.8%	<.001
Hypertension	60.6%	57.3%	67.8%	68.5%	73.3%	<.001
Diabetes mellitus	28.3%	25.4%	33.1%	37.4%	38.7%	<.001
Previous angina	53.3%	39.8%	84.7%	86.1%	91.5%	<.001
Previous MI	35.7%	23.0%	65.1%	67.3%	73.0%	<.001
Previous HF	11.1%	9.2%	11.9%	19.4%	19.6%	<.001
Previous TIA or stroke	9.6%	8.8%	10.2%	13.5%	12.7%	<.001
Heart rate, beat/min*	76 (65-90)	78 (66-92)	71 (62-86)	74 (64-90)	72 (62-86)	<.001
Systolic blood pressure, mm Hg*	146 (128-165)	147 (130-167)	142 (124-160)	143 (124-163)	145 (127-162)	<.001
Diastolic blood pressure, mm Hg*	80 (70-91)	81 (70-93)	78 (68-89)	77 (66-87)	76 (68-87)	<.001
Killip class						.004
I	84.0%	84.2%	85.6%	80.2%	82.9%	
II	11.3%	11.0%	10.7%	13.9%	12.5%	
III/IV	4.7%	4.8%	3.7%	5.9%	4.6%	
Cardiac arrest	0.7%	0.8%	0.3%	0.7%	0.2%	.041
ST depression	27.5%	28.5%	21.3%	30.4%	26.4%	<.001
T-wave inversion	20.3%	20.5%	17.1%	22.8%	20.7%	.001
Abnormal cardiac biomarker	44.1%	49.3%	29.2%	34.3%	30.6%	<.001
Serum creatinine, $\mu\text{mol/L}$ *	89 (75-109)	88 (74-107)	89 (75-108)	97 (80-121)	97 (78-120)	<.001
GRACE risk score*	119 (96-147)	119 (96-148)	113 (93-137)	129 (106-156)	122 (101-148)	<.001

Data are given as percentage of each group unless indicated otherwise. GRACE risk score could not be determined in 9.7% of patients due to missing data. HF, Heart failure; TIA, transient ischemic attack.

* Data are presented as median (25th-75th percentile).

performed using SPSS version 15.0 (SPSS Inc, Chicago, IL). A 2-sided P value of $<.05$ was considered statistically significant.

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Results

Study population characteristics

Baseline demographic and clinical characteristics of 12,483 patients with NSTEMI-ACS, divided into 4 groups according to prior coronary revascularization status are shown in Table I. Of the 12,483 patients, 8,884 (71.2%) of patients had no prior revascularization, 1,773 (14.2%) had PCI only, 1,193 (9.5%) had CABG only, and 633 (5%) had both PCI and CABG. Overall, the median (25th-75th percentile) GRACE risk score was 119 (96-147).

Compared to the no prior PCI/CABG group, patients in the PCI only, CABG only, and PCI and CABG groups were more likely to be men, with higher prevalence rates of hypertension, diabetes, dyslipidemia,

previous angina, heart failure, and MI all $P < .001$ for 4-group comparisons).

Medication use within the first 24 hours of admission

Table II summarizes the use of antiplatelet and antithrombin medications within the first 24 hours of admission in patients stratified by coronary revascularization status. Compared to the other groups, patients with previous CABG were less likely to receive antiplatelet and antithrombin therapies, except unfractionated heparin.

In-hospital outcomes

Table III compares the unadjusted rates of in-hospital mortality and the composite of death/myocardial reinfarction among 4 groups. The rates were highest in the group without prior revascularization ($P < .001$).

In-hospital procedures

Table III shows the in-hospital use of cardiac procedures in the 4 groups. The rates of cardiac catheterization and PCI were lowest among patients with history of CABG (45.2% and 18.0%, respectively) and highest in those who had prior PCI only (57.9% and 30.4%, respectively). The time to cardiac catheterization was also longer for patients with prior CABG. After adjusting

Table II. Medication use in the first 24 hours of admission according to prior revascularization status

Medication use within the first 24 h of admission	Overall (n = 12483)	No prior PCI/CABG (n = 8884)	Prior PCI only (n = 1773)	Prior CABG only (n = 1193)	Prior PCI and CABG (n = 633)	P (4-group comparison)
Aspirin	91.8%	92.0%	92.4%	89.5%	91.5%	.02
Ticlopidine/clopidogrel	49.3%	47.2%	60.0%	44.0%	58.3%	<.001
Heparin (any)	88.1%	88.7%	86.5%	86.2%	87.5%	.08
UFH	33.8%	33.9%	32.1%	35.8%	33.1%	.23
LMWH	56.0%	56.4%	56.5%	52.2%	56.1%	.05
Glycoprotein IIb/IIIa inhibitor	6.9%	7.2%	6.4%	5.2%	7.0%	.08

UFH, Unfractionated heparin; LMWH, low-molecular-weight heparin.

Table III. In-hospital procedures and outcomes by prior coronary revascularization status

Procedure/outcome	Overall (n = 12483)	No prior PCI/CABG (n = 8884)	Prior PCI only (n = 1773)	Prior CABG only (n = 1193)	Prior PCI and CABG (n = 633)	P (4-group comparison)
Cardiac catheterization	54.3%	55.0%	57.9%	45.2%	51.6%	<.001
Time to cardiac catheterization (d)*	3 (2-6)	3 (2-5)	3 (2-5)	4 (2-7)	4 (2-6)	<.001
PCI	26.2%	26.3%	30.4%	18.0%	28.9%	<.001
CABG	4.9%	5.5%	4.6%	2.1%	2.0%	<.001
Any revascularization (PCI or CABG)	30.6%	31.3%	34.7%	19.9%	30.3%	<.001
Death	1.9%	2.3%	0.7%	1.7%	0.9%	<.001
In-hospital death/myocardial (re-)infarction	5.7%	6.4%	3.9%	3.9%	4.8%	<.001

Data are presented as percentage unless indicated otherwise.

* Median (25th-75th percentile).

Table IV. Independent predictors of cardiac catheterization during index hospitalization

Independent predictor	Adjusted odds ratio (95% CI)	P
Registry		
ACS I	Reference	
ACS II	2.74 (1.71-4.38)	<.001
GRACE/expanded-GRACE	2.54 (1.59-4.06)	<.001
GRACE risk score		
Low	Reference	
Intermediate	0.83 (0.72-0.95)	.009
High	0.46 (0.37-0.57)	<.001
On-site cardiac catheterization facilities	3.96 (2.65-5.91)	<.001
Prior HF	0.51 (0.44-0.60)	<.001
Prior MI	0.68 (0.58-0.79)	<.001
Prior stroke	0.60 (0.50-0.72)	<.001
Female sex	0.73 (0.65-0.82)	<.001
Coronary revascularization status		
No previous PCI/CABG	Reference	
Previous PCI*	1.18 (1.04-1.34)	.008
Previous CABG*	0.77 (0.68-0.87)	<.001

* P for interaction between previous PCI and previous CABG = 0.93.

for possible confounders, the independent negative predictors of in-hospital cardiac catheterization were high and intermediate GRACE risk scores, previous CABG, prior heart failure, MI, stroke, and female sex

(Table IV). Conversely, previous PCI was independently associated with cardiac catheterization during index hospitalization. There was no significant interaction ($P = .93$) between previous PCI and CABG. The model c-statistic was 0.72, and Hosmer-Lemeshow goodness-of-fit test P value was .71, indicating adequate discrimination and fit, respectively. Sensitivity analysis excluding patients who died within 48 hours of admission ($n = 56$) provided similar results.

Discussion

In this large observational study, we found that patients with history of PCI presenting with NSTEMI-ACS were more likely to be managed invasively, which is consistent with the current guideline recommendations.⁴ Conversely, despite guideline recommendations, patients with previous CABG who were older, presented with worse Killip class and higher GRACE risk score, less frequently underwent cardiac catheterization and revascularization. Furthermore, early use of evidence-based medications was lower in the group with prior CABG only. These findings suggest that physicians may underuse evidence-based medical and invasive therapies for patients with previous CABG.

With the increased availability and use of invasive cardiac procedures in the past decade, a history of coronary revascularization among ACS patients is

becoming more prevalent. Observational studies based on selected clinical trial populations have demonstrated worse clinical outcomes of patients with previous CABG compared to those without history of CABG.²⁰⁻²³ However, there are limited data on the management patterns in relation to previous coronary revascularization status in the “real world.”

Several landmark studies¹⁻³ have shown the benefits of an early invasive strategy in high-risk patients with NSTEMI-ACS, as reflected in the current guidelines.⁴ However, FRISC II¹ and RITA-3³ excluded patients with prior CABG and in the TACTIC-TIMI 18 study,² patients with CABG within the prior 6 months were excluded. Furthermore, the more recent ICTUS trial²⁴ included only a small number of CABG patients (8.7%), and it failed to prove superiority of an early invasive strategy to a selective invasive strategy in patients with NSTEMI-ACS and elevated troponin. Thus, there appears to be a lack of conclusive evidence to guide the use of invasive strategy in the management of NSTEMI-ACS patients who have prior CABG.

Several observational studies have examined the relationship between invasive treatment and outcome in patients with previous CABG. Gurfinkel et al²⁵ evaluated the in-hospital and 6-month outcome of 3,853 ACS patients with prior CABG. Of these patients, 497 patients underwent invasive treatment within 48 hours of admission, whereas 3,356 were managed noninvasively. There was no statistically significant difference in hospital outcomes (primary composite of death, nonfatal MI, and recurrent ischemia) between the invasive and noninvasive treatment groups. However, 6-month mortality rate was significantly lower in the invasive group compared to the noninvasive group. Patients treated invasively experienced higher readmission rates and repeat cardiac procedures but lower incidence of cardiac events after 6 months. Similarly, in the GUSTO IV study, coronary revascularization within 30 days of admission was associated with reduced 1-year mortality in NSTEMI-ACS patients.²⁶ However, of the 2,265 patients who underwent revascularization within 30 days, only 9% had a history of CABG. In a large Swedish registry study of 10,837 patients <80 years old who had previous CABG,²⁷ revascularization within 14 days of hospital admission for NSTEMI-ACS was associated with a marked reduction in 1-year mortality (5.4% vs 13.1%).

There is also limited evidence to support the routine use of an early invasive strategy specifically in the management of ACS patients with prior PCI. The prevalence of previous PCI in the ICTUS trial was 11.7%, and in TACTIC-TIMI 18, PCI within 6 months was an exclusion criterion. In a post hoc analysis of 3 clinical trials (GUSTO IIb, PURSUIT, PARAGON-B), 3,012 patients with prior PCI and 21,154 patients without prior PCI who presented with NSTEMI-ACS were assessed for 30-day and 180-day outcomes. Significantly lower mortality rates at 30 days and 180 days were observed in the prior PCI

group.²⁸ In the present study of less selected ACS patients, the group with prior PCI had lower unadjusted rates of in-hospital mortality and death/(re-)MI. In contrast, Sanchis et al²⁹ found that prior PCI is an adverse prognosticator among NSTEMI-ACS patients with normal troponin levels.

Our study shows that history of CABG was associated with lower use of aspirin, thienopyridine, and GP IIb/IIIa inhibitors compared with the other groups. Aspirin and clopidogrel are the cornerstones for both invasive and conservative management of ACS patients.⁴ The Clopidogrel in Unstable angina to prevent Recurrent Event (CURE) trial,³⁰ which demonstrated the efficacy of clopidogrel, included patients with prior revascularization (17.9%). Those patients in fact derived an even greater benefit (hazard ratio 0.56 vs 0.88, *P* for interaction = .002), although this subgroup analysis combined patients with prior CABG and those with prior PCI. In the present study, clopidogrel was significantly underused in the group with previous CABG only. Similarly, GP IIb/IIIa inhibitors reduce the rates of death and MI in ACS patients undergoing PCI.^{31,32} Several subgroup analyses have specifically assessed the benefit of GP IIb/IIIa inhibitors in patients with prior CABG.^{22,33} Labinaz et al²² assessed the 30-day and 180-day outcomes of 1,134 patients with prior CABG enrolled in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression with Integrilin Therapy (PURSUIT) Trial. Although patients with prior CABG had higher mortality rate at 30 days and at 180 days than those without CABG, the effect of eptifibatide appears to be similar on primary end point of death or MI in both groups. In another subgroup analysis, Servoss et al³³ assessed the effect of tirofiban on the outcomes of patients with previous CABG presenting with ACS in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial. Among patients with prior CABG, compared to heparin alone, tirofiban, and heparin reduced the incidence of death, MI, or refractory ischemia at 7 and 30 days. Together, these data suggest that patients with previous CABG may derive similar benefits from these evidence-based therapies. Thus, our findings imply a disparity between evidence and practice in the medical treatment of ACS patients with prior CABG.

Although the present study identifies important gaps in the management of ACS patients with prior revascularization, the underlying reasons remain to be determined. Of note, the patients with prior CABG were more likely to be older, with higher rates of diabetes mellitus, heart failure, cerebrovascular disease, and renal dysfunction. These comorbidities may deter physicians from recommending more intensive treatment,^{18,19} although the independent association between prior CABG and lower use of cardiac catheterization was maintained even after controlling for these factors. Nevertheless, these higher

risk patients may derive a greater absolute therapeutic benefit, so that the risk-benefit ratio may be favorable, at least among carefully selected patients. It is also possible that the underrepresentation or exclusion of patients with previous revascularization in major clinical trials may have contributed to the lower use of these therapies by physicians.

Study limitations

Although recruitment of consecutive patients was encouraged in all 3 registries, this could not be verified. Second, we did not collect data on coronary anatomy and the time of prior revascularization. For example, ACS patients with prior CABG and recent cardiac catheterization showing coronary anatomy not amenable to repeat revascularization would be treated conservatively. Third, we did not consider the patient preference for treatment. It is possible that due to higher procedural risk for revascularization (especially surgical), patients with prior CABG might prefer conservative medical treatment. Fourth, despite applying statistical methods that attempt to adjust for potential confounders, we may not have accounted for all the measured and unmeasured characteristics that may contribute to the physicians' decisions to not proceed with an invasive strategy and/or administer certain medical therapies. Fifth, the mortality rate was low because early deaths might have been excluded (due to the need for informed consent). Finally, we did not evaluate long-term outcomes in relation to revascularization, although this has been the focus of previous studies.

Conclusions

Despite current guidelines recommendations and a higher risk profile, ACS patients with prior CABG were less likely to receive evidence-based medical and invasive therapies. Conversely, patients with previous PCI are more likely to receive intensive medical and invasive therapies, compared to the CABG group. More definitive data from randomized controlled trials may help to guide the optimal treatment of these ACS patients. Furthermore, quality improvement measures to ensure proper implementation of up-to-date management guidelines in the "real world" are warranted.

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